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MCKEE, VOORHEES & SEASE, P.L.C.
801 GRAND AVENUE
SUITE 3200
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EXAMINER

HUYNH, PHUONG N

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 14

Application Number: 09/772,603
Filing Date: January 30, 2001
Appellant(s): YODER ET AL.

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Edmund J. Sease
For Appellant

EXAMINER'S ANSWER

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

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(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellants' statement of the issues in the brief is partially correct.

Appellants' brief presents arguments relating to (A) whether claims 8-10 unpatentable since the numbering of the claim is not in the left margin and in view of the blank on page 5, line 8 of the specification. This issue relates to formality of the specification and not to appealable subject matter.

The rejection of Claim 8 under 35 U.S.C. 112, second paragraph, is hereby withdrawn in view of Appellants' argument that "mammal" has a commonly understood meaning, and the disclosure of domesticated livestock animals in paragraph bridging pages 5 and 6 of the specification. The Office assumes that "a mammalian species" is meant to be "a mammal".

The rejection of Claim 8 under 35 U.S.C. 112, second paragraph, is hereby withdrawn in view of Appellants' argument that the present invention is effective against both bacteria and viruses and the specification discloses that the IgG fraction has bacterial static and viral static activity in tissue culture.

(7) Grouping of Claims

Appellants' brief includes a statement that claims 8-10 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,096,310	Bier	8-2000
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5,871,731	Sprotte	2-1999
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Kempf, C. "Virus Inactivation during Production of Intravenous Immunoglobulin" *Transfusion*, Vol 31, No. 5 (1991), pp. 423-427

(10) *Grounds of Rejection*

The following ground of rejection is applicable to the appealed claims:

Claim Rejections - 35 USC § 103

Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,096,310 (Filed April 1997, PTO 892) or US Pat No. 5,871,731 (Feb 1997, PTO 892) each in view of Kempf *et al* (Transfusion 31(5): 423-27; 1991).

The '310 patent teaches a method of providing bacterial static activity wherein the reference method provides oral dosing of a mammalian species such as humans, cow, goats, sheep, and pigs with an anti-bacterial effective amount of isolated immunoglobulin (IgG) such as bovine gamma globulin that stop gastrointestinal bacterial overgrowth (See abstract, claims 1-2 of '310 patent, in particular). The '310 patent further teaches that the reference immunoglobulin (IgG) is administered orally in variable doses between about 100 mg and about 600 mg of protein in 15 ml three times a day (See column 4, lines 50-56, column 4, lines 65, in particular) or between about 100 mg and about 1,800 mg per day (See claim 4 of '310 patent) or about 1.8 g/day (1800 mg x 1 g per 1000 mg).

The '731 patent teaches a method of providing bacterial static activity such as campylobacter jejuni (See column 3, line 15-18, in particular) wherein the reference method provides oral dosing of a mammalian species such as humans with an anti-bacterial effective amount of purified human immunoglobulin (IgG) at dosages from 1 to 20 g per day, for treatment of chronic pain associated with bacterial exposure (See abstract, column 3, line 15-18, column 4, lines 36-37, claims 1-5, in particular). The '731 patent further teaches that the reference immunoglobulin can be administered via other routes such as intravenously at 5 to 10 g per day (see column 4, line 43, in particular). The reference method of oral or intravenous administration of IgG is useful for soothing pain associated with bacterial infection.

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The claimed invention as recited in claims 8 differs from the teachings of the references only that the method wherein the immunoglobulin is an IgG fraction which has been treated by acid hydrolysis, heated from 15 minutes to 1.0 hour at a temperature of 35°C to 40°C and thereafter neutralized.

Kempf *et al* teach a method of preparing IgG fraction by acid hydrolysis with HCl at (pH 4), heated at a temperature of 37°C (Fig 1, page 424 column 2, Virus inactivation, in particular) for various times such as 1 hour (see Fig 3, in particular) and then neutralized with NaOH to inactivate a variety of viruses (to abolish their infectivity) such as human immunodeficiency virus, herpes simplex virus type 1, human cytomegalovirus, Semiliki Forest viruses (See Abstract, Fig 1, Table 1, in particular). After inactivation by acid hydrolysis, the reference acid hydrolyzed IgG fraction has viral static activity toward virus such as Vesicular stomatitis viruses (VSV), which is known to be transmitted orally and causes food and mouth disease in live-stocks, by reducing the viral titer of Vesicular stomatitis viruses (VSV) from initial titer of 5.5×10^6 to 3.9×10^6 (See page 424, column 1, last paragraph in virus inactivation, column 2 in Table 1 for before inactivation and column 3 in Table 1 for after inactivation, in particular) using the established method such as the plaque assay on Vero cells (See page 424, left column, last paragraph in Virus inactivation, in particular). In fact, the specification on page 10 discloses the use of Vero cells to test viral static activity and the specification on page 5 third full paragraph discloses the same procedure such as acid hydrolysis with HCl at 37°C for an hour and then neutralize with NaOH as taught by Kempf *et al*. Kempf *et al* teach that transmission of viruses such as HIV, and hepatitis B (also known to transmit orally) and C viruses by immunoglobulin is highly risky (See page 423, column 1, in particular) and the reference method is useful for inactivating a variety of viruses for intravenous injection and that inactivation of VSV (transmitted orally) requires both a low pH and an elevated temperature because virus titer dropped by approximately 4 orders of magnitude after incubation with HCl at pH 4 and 37°C (See Abstract, page 425, left column, Inactivation of VSV, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inactivate any IgG preparation and test for bioactivity as taught by Kempf *et al* for oral dosing as taught by the '310 patent or the '731 patent by treating any IgG preparation with acid hydrolysis such as HCl, heated at 37°C for one hour and then neutralized with NaOH as taught by Kempf *et al* for a method of providing bacterial and viral static activity. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to do this because Kempf *et al* teach that transmission

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of viruses such as HIV, and hepatitis B (which can also be transmitted orally) and C viruses by immunoglobulin (IgG) is highly risky (See page 423, column 1, in particular) and treating any IgG by acid hydrolysis such as HCl at 37°C for an hour and neutralized thereafter with NaOH is useful to inactivate a variety of viruses (See page 424, column 1, last paragraph in virus inactivation, column 2 in Table 1 for before inactivation and column 3 in Table 1 for after inactivation, in particular). The reference IgG fraction after viral inactivation has viral static activity which could readily be determine by one of ordinary skill in the art using the established method such as the plaque assay on Vero cells (See page 424, left column, last paragraph, in Virus inactivation, in particular). The '310 patent teaches oral dosing of a mammalian species such as humans, cow, goats, sheep, and pigs with bovine immunoglobulin (IgG) is useful for stopping gastrointestinal bacterial overgrowth (See abstract, claims 1-2 of '310 patent, in particular). The '731 patent teaches human IgG could be administered orally or intravenously and that IgG is useful for soothing pain associated with bacterial infection. The recitation of IgG fraction in claim 8 is within the teachings of Kempft et al because acid treatment hydrolyzes any IgG molecule to generate IgG fraction. The claimed method and the reference method begin with the same whole IgG molecule as the starting material, and go through the same process of acid hydrolysis and neutralize thereafter. Thus the end product such as the IgG fraction is obviously the same.

(11) Response to Argument

At page 7, part 1 of the Brief, Appellants argue that it is not obvious to combine the teachings of the prior art to produce the claimed invention.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Kempft *et al* pertain to transmission of viruses such as HIV, and hepatitis B and C viruses by immunoglobulin transfusion (intravenous administration) is highly risky (See page 423, column 1, in particular). To avoid viral transmission, it is clear from the teachings of Kempft et al that one should inactivate virus during immunoglobulin preparation by acid hydrolysis at (pH 4) with HCl, heated at a temperature of 37°C (Fig 1, page 424 column 2, Virus inactivation, in particular) for various times such as 1 hour (see Fig 3, in particular) and then neutralized with NaOH (See page 424, Virus inactivation, in particular) prior to

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therapeutic use. Kempf *et al* further teach the reference acid hydrolyzed IgG fraction after inactivation has viral static activity such as reducing the viral titer of Vesicular stomatitis viruses (VSV), which is known to be transmitted orally and causes food and mouth disease in live-stock, from initial titer of 5.5×10^6 to 3.9×10^6 (See page 424, column 1, last paragraph in virus inactivation, column 2 in Table 1 for before inactivation and column 3 in Table 1 for after inactivation, in particular) using the established method such as the plaque assay on Vero cells (See page 424, left column, last paragraph in Virus inactivation, in particular). In fact, the specification on page 5, third full paragraph discloses the same procedure as taught by Kempf *et al*. The teachings of Kempf *et al* differ from the claimed invention only that the IgG is administered orally to provide bacterial and viral static activity in a mammal. The '310 patent teaches a method of providing bacterial static activity wherein the reference method provides oral dosing of a mammalian species such as humans, cow, goats, sheep, and pigs with an anti-bacterial effective amount of isolated immunoglobulin (IgG) such as bovine gamma globulin that stops gastrointestinal bacterial overgrowth (See abstract, claims 1-2 of '310 patent, in particular). The '731 patent teaches a method of administering IgG such as human IgG either orally or intravenously to a mammalian species such as humans with an anti-bacterial effective amount of purified immunoglobulin (IgG) at dosages from 1 to 20 g per day, for treatment of chronic pain associated with bacterial exposure (See abstract, column 3, line 15-18, column 4, lines 36-37, claims 1-5, in particular). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inactivate and test the bioactivity of virus growth in any IgG preparation by treating any IgG preparation with acid hydrolysis such as HCl, heated at 37°C for one hour and then neutralized with NaOH taught by Kempf in the IgG preparation employed by the '310 patent and the '731 patent. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the clean IgG fraction as taught by Kempf. The strongest rationale for combining references is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), See MPEP 2144.

At page 8, part 2 of the Brief, Appellants argue that the IgG fraction that has been acid hydrolyzed for 15 to 60 minutes at 35-40 °C, then neutralized is significantly different from the intact IgG protein and having a significant different molecule weight. The new protein has been found to be bacterial static (slow the growth of bacteria) as well as virus in tissue cultures.

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In response to Appellants' argument, it is scientifically well established that acid hydrolysis of whole IgG inherently produces an IgG fraction having a lower molecular weight than the whole, unmodified protein and also admitted by Appellants' argument on page 8 of the Brief. Kempf *et al* teach, as early as 1991, a method of preparing IgG fraction by mild acid hydrolysis at (pH 4) with HCl, heated at a temperature of 37°C (Fig 1, page 424 column 2, Virus inactivation, in particular) for various times such as an hour (see Fig 3, in particular) and neutralized thereafter with NaOH. After inactivation by acid hydrolysis, the reference acid hydrolyzed IgG fraction has viral static activity toward viruses such as Vesicular stomatitis viruses (VSV), which is known to be transmitted orally and causes foot and mouth disease in livestock, by reducing the viral titer of Vesicular stomatitis viruses (VSV) from initial titer of 5.5×10^6 to 3.9×10^6 (See page 424, column 1, last paragraph in virus inactivation, column 2 in Table 1 for before inactivation and column 3 in Table 1 for after inactivation, in particular). As is evident in the specification on page 5, lines 9-12, the starting material from which the IgG fraction may be derived from bovine or porcine blood. The IgG is acid hydrolyzed with HCl for an hour at a temperature of from 35 to 40 C (page 5, line 15-18 of the specification). The claimed method and the reference method clearly begin with the same whole IgG molecule as the starting material, and go through the same process of acid hydrolysis. Obviously, the end product such as the IgG fraction would be the same.

At page 9, first paragraph of the Brief, Appellants argue that the '310 patent and the '731 do not teach oral administration of an acid hydrolyzed, heated, and neutralized IgG fraction as required by Appellant's claims.

In response to Appellants' argument against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection would have been under 35 USC § 102(b) if the '310 patent and the '731 each teach every limitation such as oral administration of an acid hydrolyzed, heated, and neutralized IgG fraction in the claims. Because the '310 patent and the '731 do not teach the elements of acid hydrolyzed, heated, and neutralized IgG fraction, the claims are rejected under 35 USC § 103.

In the paragraph bridging page 9 and page 10 of the Brief, Appellants argue that Kempf *et al* teaches intravenous immunoglobulin and describes a method of inactivating viruses in immunoglobulin prior to intravenous administration in order to improve their safety. The Appellants also state that there

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would have been no incentive for a person skilled in the art at the time of Appellants' invention to use the Kempft method of treating immunoglobulin for intravenous administration in a method for oral dosing of immunoglobulin, as taught by the '310 patent and the '731 patent. Moreover the Appellants argue that it is scientifically well established that transmission of virus such as HIV, hepatitis B and hepatitis C is through blood to blood (intravenously) or semen to blood contact.

Contrary to Appellants' assertion that there is no incentive to use the method of Kempft et al to inactivate the virus growth in any IgG preparation for oral administration, it is clearly established by Kempft et al and the Food and Drug Administration (FDA) that viruses such as hepatitis B and C may be present in the plasma (see page 423, column 1, in particular) and any immunoglobulin preparation for therapeutic use clearly has the potential risk of viral transmission (See page 423, column 1, in particular). After inactivation by acid hydrolysis, Kempft et al teach that the reference acid hydrolyzed IgG fraction has viral static activity toward virus such as Vesicular stomatitis viruses (VSV), which is known to transmit orally and causes food and mouth disease in live-stocks, by reducing the viral titer of Vesicular stomatitis viruses (VSV) from initial titer of 5.5×10^6 to 3.9×10^6 (See page 424, column 1, last paragraph in virus inactivation, column 2 in Table 1 for before inactivation and column 3 in Table 1 for after inactivation, in particular) using the established method such as the plaque assay on Vero cells (See page 424, left column, last paragraph in Virus inactivation, in particular). Further, it is clearly established by the '310 patent that IgG from human donors are potential carriers of very serious vectors, including HIV and hepatitis (See column 4, line 51-52, in particular). In fact, the claimed method as disclosed on page 5 of the specification and the method of Kempft et al clearly begin with the same whole IgG molecule as the starting material, and go through the same process of acid hydrolysis such as treating with HCl (Fig 1, page 424 column 2, Virus inactivation, in particular) heated at 37 °C for various times such as 1 hour (see Fig 3, in particular) and then neutralized with NaOH (See page 424, column 1 Virus inactivation, in particular). Further, the instant specification on page 11 clearly discloses feeding acid-treated IgG to chicken. One skilled in the art would have been motivated at the time the invention was made to use the Kempft's method to treat the IgG employed by the '310 patent or the '731 patent to inactivate any viruses in any IgG preparation prior to therapeutic use either orally or intravenously for safety reasons. Contrary to Appellants' assertion that transmission of virus such as HIV, hepatitis B and hepatitis C is through blood to blood (intravenously) or semen to blood contact, it is scientifically well established at the time the invention was made that hepatitis B is also transmitted orally. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inactivate any virus contamination such as (HIV, hepatitis B, VSV) before orally administering the therapeutic compound.

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At page 10 first paragraph of the Brief, Appellants argue that the '310 patent teaches away from its combination with Kempf et al since the '310 patent notes that the use of immunoglobulin from animal is advantageous since animals such as cows, horses, pigs, sheep and goats do not carry "very serious disease vectors, including hepatitis and HIV". Thus, since the source of the '310 patent immunoglobulin is already "safe" there would be no motivation whatsoever for a person skilled in the art to combine its teachings with the viral inactivation methods of Kempf et al.

Contrary to Appellants' assertion that the '310 patent teaches away from its combination with Kempf et al, the '310 patent teaches the advantages of using animal derived immunoglobulin, in particularly cow, sheep, goat, pig or horse immunoglobulins, over human immunoglobulins are: (1) animal immunoglobulins are more readily accessible, and (2) animal immunoglobulins are relatively safer than human donor. However, animal antibodies still have the potential of carrying other animal viruses because it is also fairly assumed that these animals have been exposed over their lifetime to the same range of potential pathogens as human patients (See column 2, lines 46-60, in particular). The '310 patent further teaches "safety and cost of the immunoglobulin treatment are of paramount importance for patients who may continue the immunoglobulin treatment for a long period of time" (See column 2, lines 60-65, in particular). In fact, the specification on page 5 lines 9-12, clearly states that the starting material from which the IgG fraction is derived is from bovine or porcine blood serum. The general allegation by Appellants that the immunoglobulin as taught by the '310 patent is already 'safe' is unfound because animal antibodies still have the potential of carrying other animal viruses.

For the above reasons, it is believed that the rejections should be sustained.

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Respectfully submitted,


Phuong N. Huynh, Ph.D.


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Conferees
Christina Chan
SPE, Art unit 1644

James Housel
SPE, Art unit 1648

ZARLEY MCKEE THOMTE VOORHEES & SEASE PLC
SUITE 3200
801 GRAND AVENUE
DES MOINES, IA 50309-2721


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600


JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600